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MODULATION OF THE FREQUENCY OF HUMAN CYTOMEGALOVIRUS-INDUCED CHROMOSOME ABERRATIONS BY CAMPTOTHECIN

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ABSTRACT The effects of selected DNA repair inhibitors on the frequency of human cytomegalovirus (HCMV)-induced chromosome aberrations in human peripheral blood lymphocytes (PBLs) were evaluated. Treatment of HCMV-infected PBLs with camptothecin (0.05 to 0.3 μg/ml), an inhibitor of topoisomerase I, for 30 hr resulted in a significant ($P<0.01$) synergistic enhancement of the frequency of HCMV-induced chromosome damage. on the other hand, a significant increase in the frequency of chromosome damage was not noted for infected PBLs treated with either 3-aminobenzamide (3-AB) (3 to 30 μg/ml), an inhibitor of poly (ADP-ribose) polymerase, or novobiocin 3 to 30 μg/ml) an inhibitor of topoisomerase II or excision repair processes for 30 hr. chromatid-type breaks including chromosome exchanges were the predominant type of chromosome aberrations observed in the HCMV-infected cells treated with camptothecin suggesting that HCMV infection is associated with the induction of single-strand DNA breaks. Furthermore, these findings suggest that HCMV infection does not inflict direct DNA damage which is repaired through 3-AB- or novobiocinsensitive pathways.

Human cytomegalovirus (HCMV) is a common pathogen which infects about 80% of the world's population causing, for the most part, persistent subclinical infections (Weller, 1971). A relatively small percentage of otherwise healthy immunologically competent people experience clinical HCMV disease (Cohen *et al.*, 1986). Generalized HCMV infection, however, is the bane of individuals whose immune system is compromised (Schooley, 1990; Rubin, 1990). Molecular epidemiological studies strongly suggest that HCMV is one of the most frequent cause of congenital infections and that these infections result in a high incidence of birth defects and developmental abnormalities (Alford *et al.*, 1990). Several studies (Nachtigal *et al.*, 1978; Lulci *et al.*, 1980; AbuBakar *et al.*, 1988) have shown that HCMV infection can result in an increase in the frequency of chromosome aberrations. Since the ability to cause chromosome damage may be significant in the induction of birth defects and possibly in HCMV-induced malignancy, we undertook the present investigation to evaluate the mechanisms by which HCMV may cause chromosome damage. In this study, the effects of selected DNA repair inhibitors on the frequency of HCMV-induced

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chromosome aberrations were evaluated. The results indicate that the presence of camptothecin, but not 3-aminobenzamide (3-AB) ro novobiocin, results in a concentration-dependent increase in the frequency of chromosome aberrations in HCMV-infected peripheral blood lymphocytes (PBLs). Accordingly, it is proposed that HCMV-induced chromosome damage in PBLs does not substantially involve DNA repair activities sensitive to inhibition of poly ADP-ribosylation or excision repair processes, but is related to camptothecin-sensitive DNA repair, conceivably involving the activity of topoisomerase I.

MATERIALS AND METHODS

Preparation of virus stocks

HCMV strain AD169 propagated in our laboratory as previously described (Albrecht *et al.*, 1980) was used for these studies. Briefly, confluent cultures of human embryonic lung (LU) fibroblasts were infected at a multiplicity of infection (MOI) of about 0.01－0.05 plaque forming unit (PFU)/cell. Infected cell cultures were incubated at 37℃ for 8－11 days. Afterwards, the growth medium were decanted and reserved. Infected cells were dissociated with a rubber policeman, collected by sedimentation, and sonicated to release cell-associated virus. The sonicate was clarified by sedimentation and combined with the reserved fluids (virus stock). Virus stocks were stored at -80℃ until used. The infectivity of virus stocks was determined by plaque assay (Albrecht and Weller, 1980) and was in the **Infection of** range of 6×10^6 to 1.5×10^7 PFU/ml.

Human PBLs

Whole blood obtained from healthy donors was cultured in 15 ml centrifuge tubes using RPMI 1640 medium supplemented with 10% heat-inactivated fetal calf serum (FCS) and 0.3 g/L glutamine (growth medium). PBLs were stimulated to proliferate by adding phytohemagglutinin (PHA; 0.18 mg/ml; Burroughs-Wellcome, Research Triangle Park, NC). Twenty-four hr following stimulation with PHA, cells were separated from the culture fluids by sedimentation and the supernatant fluids were reserved. The cells were resuspended in virus stock to provide a calculated MOI of approximately 5 PFU/cell and incubated at 37℃ for 2 hr. Following virus infection, the cells were collected by sedimentation and the virus inoculum was discarded. For experiments using DNA repair inhibitors, cells were resuspended in the conditioned growth medium to which the appropriate concentration of drug was added, followed by incubation ta 37℃ for 30 hr. Mitotic cells were harvested following treatment of the cell cultures with 0.1 μg/ml colcemid (Gibco BRL, Gaithersburg, MD) and metaphase chromosome spreads were prepared as described previously in detail (Abubakar *et al.*, 1988).

Scoring chromosome aberrations and statistical analysis

Metaphase cells were scored for chromosome aberrations as previously described (Evans and O'Riordan, 1975). All statistical calculations were performed using the microcomputer implementation of the statistical software package SAS (SAS Institute, Inc., Cary, NC).

Drugs

Camptothecin, novobiocin, and 3-AB were purchased from Sigma (St. Louis, MO). Stock solutions of novobiocin and 3-AB were prepared in RPMI 1640 medium. Camptothecin stock solutions were prepared in dimethyl sulfoxide (Sigma). Stock solutions were filtered through sterile microfilters (0.1 micron) immediately prior to use and diluted further in RPMI 1640 medium to obtain working solutions. Control cell cultures were treated with a similar concentration of diluent.

RESULTS

The effect of camptothecin on the frequency of chromosome aberrations in HCMV-exposed human PBLs

In preliminary experiments we analyzed HCMV-infected PBLs treated with camptothecin, novobiocin or

3-AB for 2 hr prior to arrest of mitotic cells with Colcemid (data not shown). This treatment schedule did not result in a significant ($P<0.05$) increase in the frequency of chromosome aberrations. Since the effects of these drugs are reversible (Hsiang *et al.*, 1985; Zhang *et al.*, 1988), it was possible that, following removal of the drug, chromosome damage was repaired. Therefore, more comprehensive experiment consisting of drug treatment for 30 hr postexposure to HCMV were undertaken.

Camptothecin treatment to HCMV-exposed PBLs for 30 hr induced a significant ($P<0.05$) synergistic enhancement of the frequency of chromosome damage and the number of aberrant cells in a concentration-dependent manner (Table 1; Fig. 1). For example, HCMV infection in the absence of camptothecin

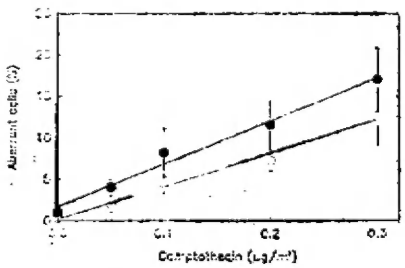

Figure 1 The effect of camptothecin on the frequency of chromosome aberrations in human peripheral blood lymphocytes that are either infected with HCMV (closed circles) or mockinfected (open circles). The error bars indicate standard deviation

resulted in 1% aberrant cells, while camptothecin treatment alone resulted in a linear increase in aberrant cells from 2.00±100% to 12.50±3.00% as the concentration was increased from 0.05 to 0.3 μg/ml. Yet, the number of aberrant cells increased from 4.33±1.03% for mock-infected cells treated with 0.1 μg/ml camptothecin to 8.17±2.93% for HCMV-infected cells treated with the same concentration of camptothecin (Table 1). The expected additive effect of combined treatment with HCMV and camptothecin would be 6.33% aberrant cells. The observed increase with combined treatment to 8.17% aberrant cells is a significant enhancement ($p<0.05$) over the expected value. For cells treated with 0.3μg/ml camptothecin, aberrant cells increased from 12.50±3.00% to 17.00±3.92% with HCMV exposure. The expected additive effect at this concentration of camptothecin (0.3 μg/ml) and HCMV infection is 13.50% aberrant cells. Therefore, the observed frequency of aberrant cells with 0.3 μg/ml camptothecin and HCMV infection also was significantly enhanced ($P<0.05$) over the expected frequency. Treatment of HCMV-exposed PBLs with camptothecin at a concentration of 0.3 μg/ml also resulted in 67, 39, and 91% significant increases ($P<0.05$) in the frequency of chromosome breaks, exchanges and deletions, respectively, relative to the expected additive effects of HCMV infection and camptothecin treatment (Table 1). The predominant type of chromosome damage observed in the camptothecin-treated, HCMV-exposed metaphase cells was chromatid-type aberrations such as chromosome breaks and exchanges. Since the enhancement of the frequency of chromosome damage did reflect the increase in the number of cells with aberrant chromosomes, these data indicate an increase in the number of aberrant chromosomes per cell, suggesting a synergistic interaction within cells that were dually exposed to HCMV and camptothecin.

The effect of novobiocin or 3-aminobenzamide on the frequency of chromosome aberrations in HCMV-exposed human PBLs

In order to ascertain the specificity of the enhancing effect of camptothecin on HCMV-induced chromosome damage we investigated also the effect of continuous treatment with either novobiocin or 3-AB at concentrations from 3 to 30 μg/ml on HCMV-infected PBLs. Neither compound resulted in a significant

Table 1 The Effect of HCMV Infection and Thirty Hour Exposure to Camptothecin on Chromosome Aberrations Frequency in Human Peripheral Blood Lymphocytes

HCMV	Camptothecin (μg/ml)	Number of cells scored	Aberrant cells % (±SD)	Type of damage per 100 cells (±SD)			
				Gaps	Breaks	Exchanges	Deletions
−	−	600	0.33	0.33	0.75	0.00	0.00
			(0.52)	(0.52)	(0.13)	(−)	(−)
+	−	600	1.00	0.50	0.83	0.00	0.17
			(0.63)	(0.00)	(0.41)	(−)	(0.41)
−	0.05	300	2.00	1.00	1.33	0.00	0.67
			(1.00)	(0.38)	(0.58)	(−)	(0.58)
−	0.1	600	4.33	1.33	3.50	0.67	0.33
			(1.03)	(0.00)	(1.38)	(0.52)	(0.52)
−	0.2	400	7.25	0.50	4.75	2.75	0.25
			(1.26)	(0.38)	(0.96)	(1.50)	(0.50)
−	0.3	400	12.50	0.25	10.25	5.75	0.75
			(3.00)	(0.75)	(5.06)	(2.22)	(1.50)
+	0.05	300	4.00	0.67	3.33	0.00	0.67
			(1.00)	(0.25)	(0.58)	(−)	(0.58)
+	0.1	600	8.17	1.00	8.83	2.83	0.33
			(2.93)	(1.25)	(4.22)	(3.49)	(0.82)
+	0.2	400	11.50	0.50	9.75	6.50	0.25
			(3.00)	(1.25)	(4.35)	(2.65)	(0.50)
+	0.3	400	17.00	1.00	18.00	8.00	1.75
			(3.92)	(1.25)	(7.35)	(5.42)	(1.50)

SD, standard deviation

Table 2 The Effect of HCMV Infection and Thirty Hour Exposure to Novobiocin or 3-Aminobenzamide on Chromosome Aberrations Frequency in Human Peripheral Blood Lymphocytes.

HCMV	Drug	Concentration (μg/ml)	Number of cells scored	Aberrant cells (%)	Type of damage (per 100 cells)			
					Gaps	Breaks	Exchanges	Deletions
−	−	−	200	0.5	3	1	0	0
+	−	−	200	1.5	3	2	0	1
−	N	3	200	1.0	1	2	0	0
+	N	3	200	3.0	1	6	0	0
−	N	10	200	1.5	1	3	0	0
+	N	10	200	2.5	1	5	0	0
−	N	30	200	1.0	4	2	0	0
+	N	30	200	4.0	1	8	0	0
−	A	3	200	2.0	1	4	0	0
+	A	3	200	1.5	4	3	0	0
−	A	10	200	1.5	1	3	0	0
+	A	10	200	1.0	4	2	0	0
−	A	30	200	1.5	4	3	0	0
+	A	30	200	1.5	3	3	0	0

A: 3-Aminobenzamide; N: Novobiocin

($P<0.05$) concentration-dependent increase in the frequency of HCMV-infected aberrant cells (Table 2). Additionally, treatment fo HCMV- ro mock-infected PBLs with 30 μg/ml of 3-AB for 30 hr demonstrated no difference in the frequency of breaks, exchanges or deletions. Similarly, novobiocin treatment of HCMV- or mock-infected PBLs resulted in an insignificant ($p<0.05$) increase in the frequency of breaks, exchanges or deletions. These data suggest that HCMV-induced aberrations are not increased by inhibition of excision-repair processes which are sensitive to inhibition by novobiocin or 3-AB.

DISCUSSION

Several hypotheses explaining how viruses may directly or indirectly cause chromosome aberrations have been advanced. These hypotheses include breakdown of lysosome membranes releasing enzymes that may cause damage (Allison *et al.*, 1965), amino acid deficiency (Paton *et al.*, 1965), interference with cellular DNA and/or protein synthesis (Nichols, 1970), and perturbation of cell physiology (AbuBakar *et al.*, 1988). How HCMV damages chromosomes, however, is not known. It is possible that HCMV may damage DNA directly by inducing DNA strand breakage (Landini *et al.*, 1982; Ripalti *et al.*, 1988). Consistent with HCMV's nicking effect on DNA is the observation that cells infected with HCMV demonstrate cytogenetic abnormalities such as breaks and produce progeny virus that has DNA which contains nicks and gaps (Geelen *et al.*, 1981).

In this study neither 3-AB nor novobiocin substantially influenced the frequency of chromosome damage in HCMV-infected cells. 3-AB inhibits the formation of poly (ADP-ribose) (ADPR) and the activity of the enzyme ADPR transferase, retarding the net resealing of DNA strand breaks which require excision repair (Shall, 1984; Boothman *et al.*, 1988). Novobiocin, on the other hand, is proposed to inhibit the pre-incision step in excision repair of damaged DNA possibly by affecting the activity of topoisomerase I (Legerski *et al.*, 1987; Dresler *et al.*, 1987). Since neither 3-AB nor novobiocin treatment significantly increased the frequency of chromosome aberrations in HCMV-infected PBLs, the present results suggest that it is unlikely that abortive HCMV infection directly damages DNA requiring excision repair processes through either 3-AB- or novobiocin-sensitive mechanisms.

It is also possible that abortive HCMV infection of human PBLs (Rice *et al.*, 1984) induces chromosome aberrations through indirect mechanisms. Enhancement of the frequency of chromosome damage in CHMV-infected PBLs treated with camptothecin in this study is consistent with inhibition of topoisomerase I (Gedik *et al.*, 1990). Camptothecin blocks the rejoining step of breakage-reunion involving topoisomerase I (Hsiang *et al.*, 1985) by trapping reversible topoisomerase I-DNA cleavable complexes (Hsiang *et al.*, 1988) which conceal single-strand DNA breaks (Mattern *et al.*, 1987). Camptothecin break sites are reported to cluster near the terminus of DNA replication (Porter *et al.*, 1989), close to the growth points of the replication forks (Avemann *et al.*, 1988). Topoisomerase I-DNA cleavable complexes were also noted to concentrate on the coding strand in the early transcription region of the SV40 genome (Jaxel *et al.*, 1988), actively transcribed human rRNA genes (Zhang *et al.*, 1988), heat shock protein (*hsp*) 70 (Rowe *et al.*, 1987), 23, 26, and 28 genes (Gilmour *et al.*, 1987), and the glucocorticoid- or CAMP-stimulated rat tyrosine aminotransferase gene (Stewart *et al.*, 1987). In the altered physiological conditions associated with HCMV infection (reviewed in Albrecht *et al.*, 1989) the fidelity of repair of single-strand DNA breaks induced by topoisomerase I during transcription or replication of the cellular DNA may be perturbed causing an increased chromosome aberration frequency. Thus, it is possible that the increase in the frequency of chromatid-type chromosome aberrations observed in the presence of camptothecin reflects inhibition of repair necessitated by HCMV-induced cellular DNA replication and/or transcriptional activation of specific cellular genes, rather than inhibition of DNA repair processes necessitated by the direct induction of DNA damage by HCMV.

This view is attractive since HCMV has been shown to stimulate cellular DNA synthesis, mitotic

activity in abortive (Albrecht *et al.*, 1976 or permissive (St. Jeor *et al.*, 1974) cells and stimulate transcriptional activation of several cell cycle-associated cellular oncogenes (*fos*, *jun*, *myc*: Boldogh *et al.*, 1990; 1991), and *hsp* 70 gene (Santomenna *et al.*, 1990). Additional work will be required to determine if the chromosome breaks observed in the metaphase cells exposed to HCMV and camptothecin are related to activation of specific cellular genes. In fact, camptothecin treatment may offer a novel method of determining which specific sites on the cellular DNA are stimulated following HCMV infection.

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喜树碱对人类巨细胞病毒诱发染色体畸变的频率的调节效应

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摘要 本文评价了所选用的DNA修复抑制剂对人类巨细胞病毒（HCMV）诱发外周血淋巴细胞（PBLs）染色体畸变频率的影响。以拓扑酶Ⅰ的一种抑制剂——喜树碱（0.05—0.3μg/ml）处理HCMV感染的人类PBLs 30小时，结果导致HCMV诱发的染色体损伤频率显著的协同性增加（$P<0.01$）。另一方面以ADP核糖聚合酶的一种抑制剂——3一氨基苯酰胺（3—AB）（3—30μg/ml），或者拓扑酶Ⅰ的一种抑制剂——新霉素（3—30μg/ml）处理HCMV感染的PBLs 30时小，染色体损伤频率未见明显增加。在喜树碱处理的HCMV感染细胞中，染色单体型断裂包括染色体交换是染色体畸变的主要类型，这提示HCMV感染与单链NDA断裂有关，这些发现还提示，HCMV感染不会造成通过3—AB或新霉素敏感途径修复的直接DNA损伤。

关键词：人类巨细胞病毒，染色体畸变，DNA修复，3-氨基苯酰胺，新霉素，喜树碱

人巨细胞病毒，